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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/934,766	BRANDENBURG ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT FOR PRIORITY, IDS, RESPONSE TO RESTRICTION REQUIREMENT, STATUS OF THE APPLICATION AND CLAIMS

1. This application is a Continuation of PCT/EP00/01530, filed 2/24/00 and claims priority under 35 U.S.C. § 119 from German Application No. 199 08041.0, filed 2/24/99. Although, the certified copies of PCT/EP00/01530 and German Application No. 199 08041.0 have not been received, priority claim is acknowledged under 35 U.S.C. § 119. The Information Disclosure Statement (IDS) and Form PTO-1449 filed 8/23/01 and the response to the restriction requirement filed 3/23/04 are acknowledged, entered and considered. Claims 15-36 are present for examination.

ELECTION WITH TRAVERSE

2. Applicant's election with traverse of Species I and Sub-species I (claims 15-17, 21, 24, 25, 28, 29, 32, 33 and 36) in Paper No. 7 is acknowledged. The traversal presented in the election has been considered persuasive for the reasons set forth in the traverse. Hence, the Office action is directed to the merits of claims 15-36 and the previous requirement for restriction has been withdrawn.

ABSTRACT MISSING

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

CLAIMS REJECTION-35 U.S.C. 112, 1st PARAGRAPH

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no description in the instant specification for the claimed **pharmaceutical preparation** nor for the **diagnostic kit** comprising an insulin analogues and additions selected from the group comprising zinc salts, phenol, m-cresol, glycerol, and other buffer substances as claimed in claims 15, 21, 22 and 23, respectively in claims 24-27 for pharmaceutical and claims 32-35 for diagnostic kit, respectively. Also, there is no description in the instant specification for the claimed **method of treating diabetes** by administering the pharmaceutical formulations of claims 24-27, respectively to a host that has diabetes as claimed in claims 28-31. The specification demonstrates synthesis of B1,B1'-Sub-[Sar^{B26}]-des-(B27-B30)-insulin-B26-amide insulin dimmer; B1,B1'-Sub-[D-Ala^{B26}]-des-(B27-B30)-insulin-B26-amide insulin dimmer; and B1,B1'-Sub-[Glu^{B26}]-des-(B27-B30)-insulin-B26-amide insulin dimmer (See e.g., Examples 1-3 of the specification). Example 4 demonstrates the biological properties for examples 1-3 of the invention. However,

there is no pharmaceutical formulations or diagnostic kits comprising the insulin analogues as claimed nor methods for treating diabetes by administering the pharmaceutical formulations of claims 24-27. There is no *in vivo* showing for the effectiveness of the insulin analogues as claimed nor there is a recognized model (identified as useful) being treated according to methods of **treating diabetes to a host** in the manner claimed in claims 28-31.

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 15-20 and 24-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite in the recitation "wherein at least one....", "...in an insulin analogue" because it is ambiguous as to the "an analogue" since in this part of the claim is the same or not as the "An analogue" in the first two (2) words of claim 15.

Claim 16 is indefinite in the recitation "characterized by" because it is unclear if it means that the formulation must be identical or not. See "comprising" instead.

Claim 16 is indefinite in the recitation "derivative thereof" because it is not clear whether it is functional or not? Appropriate clarification is required.

Claim 17 recites the limitation "the carboxylic acid group" in line 2. There is insufficient antecedent basis for this limitation in claim 15 or claim 16 or claim 17.

Claims 24-27 are indefinite in the recitation "additions". "Additions" should be a pharmaceutical carrier because it is unclear what would constitute the undefined "substances". Appropriate correction is required.

Claims 28-31 are indefinite and vague in the recitation "comprising administering the pharmaceutical....." because it is not clear what kind of administration the claims refer. It is also unclear what the intended out come of the "treatment" is supposed to be? What are the appropriate times and conditions necessary to bring about the unspecified effect of treatment? If it is intended for oral or parenteral or intradermal or other means of administration, the mode or route of administration should be recited in the claims (i.e., administering orally or intravenously or subcutaneously, etc.) is suggested.

Claims 32-35 recite diagnostic kit but are ambiguous as to what part(s) of the kit are needed for the diagnostic function. The claims are incomplete.

Claims 32-35 are indefinite in the recitation "one or more of the insulin analogues" because it is not clear how many more than one is more included or excluded. Appropriate clarification is required.

Claim 36 is indefinite in failing to recite positive active method step(s). The method for preparing claim recites "obtained, protected, reacted and isolated" which do not represent positive active method steps. Amendment of the claim to recite "obtaining, protecting, reacting and isolating) is suggested.

Claim 36 is indefinite and vague in the recitation "semisynthesis " and "method of genetic manipulation" because they are not defined in the specification and it is not

clear what the term "semisynthesis" is supposed to be? Also it is not clear what are the methods of genetic manipulation? Appropriate clarification is required.

Claim 36 is indefinite in the recitation "and/or" because it is not clear whether "and" or is it "or" is claim meant in the conjunctive or is the "/" meant to be used in the alternative. Appropriate clarification is required.

Claim 36 is indefinite in the recitation "the reaction mixture" because it is unclear as to what the mixture? Amounts of the components in the mixture? and which components? Appropriate clarification is required.

Claim 36 recites the limitation "the reaction mixture" in lines 9-10. There is insufficient antecedent basis for this limitation in claim 15 or claim 36.

CLAIMS REJECTION-35 U.S.C. § 102(b)

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Deppe et al. (Naunyn-Schmiedeberg's Archives of Pharmacology, Vol. 35, No. 2, pp. 213-217, August 1994).

Deppe et al. on page 213, right column, disclose an insulin analogue consisting of two insulin monomers covalently linked together via a bridge, wherein the insulin

monomer is an animal insulin (i.e. rat insulin) present in an insulin analogue and physiologically acceptable salts thereof. Thus, the reference discloses covalently bridged insulin monomers as claimed and as anticipates claim 15 as drafted.

7. Claims 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Leyer et al. (International Journal of Peptide & Protein Research, Vol. 46, No. 5, pp. 397-407, November 1995).

The reference of Leyer et al. discloses B1,B1'-Sub-[Sar^{B26}]-des-(B27-B30)-insulin-B26-amide insulin dimmer and B1,B1'-Sub-[D-Ala^{B26}]-des-(B27-B30)-insulin-B26-amide insulin dimmer (See e.g., abstract and page 398, right column, first paragraph) as directed to claims 21 and 22, and as such anticipates the claims as drafted.

8. Claim 36 is rejected under 35 U.S.C. 102(b) as being anticipated by Schuttler et al. (Hoppe-Seyler's Zeistchrift Fur Physiologische Chemie, Vol. 363, No. 3, pp. 317-330, March 1982).

Schuttler et al. disclose the synthesis of six isomeric insulin dimmers, linked through selected amino groups of the monomers by a dicarboxylic acid, wherein the monomers are obtained by enzyme-catalyzed semisynthesis. The monomeric insulin analogues are protected by protective groups and the monomers are isolated and purified by cellulose-acetate electrophoresis (See e.g., page 317 and 318) as directed to claim 36. Thus, the reference clearly discloses the preparation of insulin analogues

by bridging two optionally protected monomeric molecules with the preactivated dicarboxylic acid in which the monomeric analogues are obtained by enzyme-catalyzed semisynthesis, and as such anticipates claim 36 as drafted.

CLAIMS REJECTION-35 U.S.C. 103(a)

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Leyer et al. (International Journal of Peptide & Protein Research, Vol. 46, No. 5, pp. 397-407, November 1995) taken with Deppe et al. (Naunyn-Schmiedeberg's Archives of Pharmacology, Vol. 35, No. 2, pp. 213-217, August 1994).

The reference of Leyer et al. as discussed above under the rejection 102(b) discloses B1,B1'-Sub-[Sar^{B26}]-des-(B27-B30)-insulin-B26-amide insulin dimmer and B1,B1'-Sub-[D-Ala^{B26}]-des-(B27-B30)-insulin-B26-amide insulin dimmer (See e.g., abstract and page 398, right column, first paragraph).

The reference of Leyer et al. differs from claim 23 in not teaching B1,B1'-Sub-[Glu^{B26}]-des-(B27-B30)-insulin-B26-amide insulin dimmer, however, the primary reference on page 402, right column states that insulin analogues with multiple amino acid such as glycine substitutions in the region B27-B30 were chosen to show whether the side chains B27-B30 are important to retain the main–chain conformation and the ability of the hormone to self-associate. Thus, clearly motivating one of ordinary skill in the art to substitute insulin analogues with an amino acid of interest in the region of B27-B30. Further, the secondary reference of Deppe et al. discloses insulin derivatives with modifications in the regions B23-B30 were synthesized by trypsin-catalyzed coupling reactions of des-(B23-B30)-insulin with synthetic peptides (See e.g. abstract). Also, Figure 1 shows that dimmers with different length of the covalent crosslinkers were studied in order to assess the significance of the crosslinkers.

Therefore, in view of the above and in view of the combined teachings of the prior art, one of ordinary skill in the art at the time the invention was made would have

been motivated to prepare insulin by the introduction of one or a few amino acid substitutions into equivalent insulin dimmer of interest (i.e., substitution of Glu^{B26} instead of Ala^{B26} or Gly^{B26}, etc.), absent of sufficient objective factual evidence or unexpected results to the contrary.

ALLOWABLE SUBJECT MATTER

10. Claims 16-20 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitation of the base claim and any intervening claims.

11. The specific insulin analogues described in claims16-20 are free of the prior art of record.

CONCLUSION AND FUTURE CORRESPONDENCE

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 5:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

AAM Mohamed/AAM

June 11, 2004

CHRISTOPHER S. F. LOW
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